Mortality Benefit of a Blood-Based Biomarker Panel for Lung Cancer on the Basis of the Prostate, Lung, Colorectal, and Ovarian Cohort

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ABSTRACT

PURPOSE To investigate the utility of integrating a panel of circulating protein biomarkers in combination with a risk model on the basis of subject characteristics to identify individuals at high risk of harboring a lethal lung cancer.

METHODS Data from an established logistic regression model that combines four-marker protein panel (4MP) together with the Prostate, Lung, Colorectal, and Ovarian (PLCO) risk model ($PLCO_{m2012}$) assayed in prediagnostic sera from 552 lung cancer cases and 2,193 noncases from the PLCO cohort were used in this study. Of the 552 lung cancer cases, 387 (70%) died of lung cancer. Cumulative incidence of lung cancer death and subdistributional and cause-specific hazard ratios (HRs) were calculated on the basis of 4MP + $PLCO_{m2012}$ risk scores at a predefined 1.0% and 1.7% 6-year risk thresholds, which correspond to the current and former US Preventive Services Task Force screening criteria, respectively.

RESULTS When considering cases diagnosed within 1 year of blood draw and all noncases, the area under receiver operation characteristics curve estimate of the 4MP + $PLCO_{m2012}$ model for risk prediction of lung cancer death was 0.88 (95% CI, 0.86 to 0.90). The cumulative incidence of lung cancer death was statistically significantly higher in individuals with 4MP + $PLCO_{m2012}$ scores above the 1.0% 6-year risk threshold (modified χ^2, 166.27; $P < .0001$). Corresponding subdistributional and lung cancer death–specific HRs for test-positive cases were 9.88 (95% CI, 6.44 to 15.18) and 10.65 (95% CI, 6.93 to 16.37), respectively.

CONCLUSION The blood-based biomarker panel in combination with $PLCO_{m2012}$ identifies individuals at high risk of a lethal lung cancer.

ACCOMPANYING CONTENT

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INTRODUCTION

The National Lung Screening Trial provided evidence that three annual low-dose computed tomography (LDCT)–based screenings reduced lung cancer death by approximately 20% compared with chest radiography in a high-risk population.[1,2] This was verified in the NELSON trial, which also reported a reduction in lung cancer mortality from 3.3/1,000 person-years to 2.5/1,000 person-years in persons undergoing CT-based lung cancer screening (LCS).[3] Recently, the US Preventive Task Force (USPSTF) recommended broadening screening to those age 50 years and older and with a 20 pack-year (PY) history of cigarette smoking, who were either still smoking or had quit within the past 15 years.[4] Yet, the majority of individuals eligible for screening will never develop lung cancer, but may experience harms associated with LCS such as false-positive results and unnecessary follow-up procedures.[3,5-7]

Lung cancer risk prediction models have the potential to identify individuals who would benefit from LCS. To date, several lung cancer risk models have been developed, including Bach,[8] Spitz,[9] Liverpool Lung Project (LLP) and LLP Incidence Risk Models,[10,11] Hoggart,[12] Prostate, Lung, Colorectal, and Ovarian (PLCO) risk model ($PLCO_{m2012}$),[20] Pittsburgh,[13] and the Lung Cancer Risk Assessment Tool.[14] In addition to these models, the Lung Cancer Death Risk Assessment Tool (LCDRAT)[14] and the Kovalchik model[15] were developed to predict lung cancer mortality.

Incorporation of biomarkers offers additional means to personalize risk profiles. To this end, we recently performed a blinded validation study of a blood-based four-marker protein panel (4MP) consisting of the precursor form of surfactant protein B, cancer antigen 125, carcinoembryonic antigen, and cytokeratin-19 fragment (CYFRA21-1) for risk

CONTEXT

Key Objective

Can a blood-based four-marker protein panel (4MP) together with the Prostate, Lung, Colorectal, and Ovarian (PLCO) lung cancer risk model ($PLCO_{m2012}$) better identify individuals at high risk of lung cancer death compared with current US Preventive Services Task Force criteria?

Knowledge Generated

Using prediagnostic case and noncase sera from the PLCO cohort, we demonstrated that a combined 4MP + $PLCO_{m2012}$ model can identify individuals at high risk of lung cancer death, yielding an area under receiver operation characteristics curve of 0.88 (95% CI, 0.86 to 0.90). Compared with USPSFT2021 criteria, corresponding to ≥1.0% 6-year risk threshold, the combined 4MP + $PLCO_{m2012}$ model had a markedly improved subdistributional hazard ratio (HR; 9.88 [95% CI, 6.44 to 15.18] *v* 4.27 [95% CI, 3.07 to 5.94]) and lung cancer death–specific HR (10.65 [95% CI, 6.93 to 16.37] *v* 4.41 [95% CI, 3.18 to 6.14]).

Relevance *(T.E. Stinchcombe)*

This study identifies patients who are at higher risk of lung cancer mortality, and these results could assist when designing future screening and intervention studies.*

*Relevance section written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

assessment of lung cancer using prediagnostic sera from the PLCO Cancer Screening Trial. A model that combines the 4MP with the $PLCO_{m2012}$ lung cancer risk model better identified individuals at high risk of lung cancer that would benefit from LCS compared with the USPSTF 2013 and 2021 criteria.[16]

In the current study, we investigated the extent by which the 4MP and the model that combines the 4MP with $PLCO_{m2012}$ would identify individuals who are at high risk of lung cancer death in the PLCO prediagnostic cohort. Tailoring LDCT screening on the basis of an individual's predicted risk of lung cancer death has potential to maximize the benefits of screening without a disproportionate increase in potential harms.

METHODS

The PLCO Cohort

The PLCO Cancer Screening Trial was a randomized multicenter trial in the United States which aimed at evaluating the impact of early detection procedures for PLCO cancer on disease-specific mortality. A biorepository was created for blood specimens that were annually collected from consented, intervention group participants.[17] Detailed information regarding the PLCO cohort is provided elsewhere.[18]

Reporting of cancer status was based on annual questionnaires. Medical records were obtained to document diagnostic follow-up and characteristics of any diagnosed lung cancers. The TNM stage and stage group were determined by the fifth edition of the American Joint Committee on Cancer's Cancer Staging Manual. Treatment data were abstracted from medical records for the 1-year period after diagnosis. PLCO participants were followed for an additional 13 years after the PLCO study ended for lung cancer incidence and 20 years for lung cancer death.

All deaths occurring during the trial were ascertained primarily through annual study update questionnaires. Participants who did not return the questionnaire were contacted by repeat mailing or telephone. To enhance the completeness of end-point verification, the active follow-up was accompanied by periodic linkage to the National Death Index. Death certificates were obtained to confirm the death and to determine the provisional cause of death. As the underlying cause of death was not always accurately recorded on the death certificate, the PLCO trial used an end-point adjudication process to assign cause of death in a uniform and unbiased manner. All deaths with causes potentially related to cancer were reviewed by a death review committee with a nonvoting chair and three experience reviewers. Death reviewers were blinded to the trial group of the deceased participant. Lung cancer–specific deaths were defined as those with underlying cause of lung cancer or treatment for lung cancer.[19]

Risk Model on the Basis of Subject Characteristics

The $PLCO_{m2012}$ model was implemented as previously published.[20] Predictive variables in the $PLCO_{m2012}$ model were based on baseline questionnaire information and include

age, race/ethnic group, education, body mass index, chronic obstructive pulmonary disease (COPD), personal history of cancer, family history of lung cancer and smoking status (current *v* former), intensity, duration, and quit time.[20]

4MP Readouts in the PLCO Specimen Set

The specimen set consisted of sera collected preceding a lung cancer diagnosis from 552 cases and 2,193 noncase PLCO participants who did not receive a lung cancer diagnosis during the study trial or within the 13-year study follow-up period. Biomarker scores for the 4MP were calculated on the basis of the previously developed logistic regression model.[16,21] The combined model of the 4MP + $PLCO_{m2012}$ for predicting lung cancer within 1 year was developed by fitting a logistic regression with the 4MP score and the linear predictor of the $PLCO_{m2012}$[13] as two separate predictors as previously described.[16]

Statistical Analyses

Predefined weights and cutpoints on the basis of 1.0% and 1.7% 6-year risk thresholds for the 4MP score, $PLCO_{m2012}$ score, and the 4MP + $PLCO_{m2012}$ score were applied as described in our prior publication.[16] We used risk thresholds of ≥1.0% and ≥1.7% 6-year risk, which have been shown to result, respectively, in similar numbers of screening eligible individuals as the USPSTF2021 and USPSTF2013 screening criteria.[22,23] Given the limited number of cases with <10 PY smoking history in the study specimen set, we focused analyses on those participants with ≥10 PY and stratified them into low-, medium-, and high-risk groups defined by PYs and years since quitting (Data Supplement [Tables S1-S4], online only).

Strata (low-, medium-, and high-risk)–specific cutpoints for the 4MP score (1.8206 × 4MP) were estimated as described in our prior publication.[24] At the 1.0% 6-year risk threshold, respective 4MP scores >13.579, 12.529, and 12.332 for the low-, medium-, and high-risk strata were considered test-positive. At the 1.7% 6-year risk threshold, respective 4MP scores >14.117, 13.066, and 12.870 for low-, medium-, and high-risk strata were considered test-positive. For the combined 4MP + $PLCO_{m2012}$, at the 1.0% and 1.7% 6-year risk thresholds, respective scores (−11.836 + 1.6160 × 4MP + 0.9861 × [$PLCO_{m2012}$ score]) of greater than −4.595 and −4.057 were considered as test-positive.[24] For the $PLCO_{m2012}$ score, we used the logit form of $PLCO_{m2012}$ risk model.

For area under receiver operation characteristics curve (AUC) calculations, we considered all cases specimens diagnosed within 1 year of blood draw and all noncase specimens. We defined the event positive group as those individuals who died of lung cancer, whereas the event negative group consisted of participants that did not die of lung cancer (which included censored information and other causes of death). Corresponding 95% CI for statistical parameters were estimated using 1,000 bootstraps.

Survival analyses were performed among individuals with ≥10 PYs of smoking history to be consistent with the prior study.[16] In the PLCO data set, death due to causes other than lung cancer precludes the occurrence of lung cancer–specific mortality. In other words, an individual who dies of other non–lung cancer–related causes is no longer at risk of lung cancer death. Therefore, we considered alternative causes of death as competing risk events.[25] To estimate the incidence of lung cancer death over time in the presence of competing risks, we used two different modeling approaches: cause-specific hazard for lung cancer death (where nonlung cancer death is treated as a censoring event) and the subdistributional hazard of the cumulative incidence function for lung cancer death.

For the cause-specific hazard function, the instantaneous hazard function of the k^{th} event (k denotes for lung cancer death or non–lung cancer death) is defined as

$$\lambda_k^{cs} = \lim_{\Delta t \to 0} \frac{\Pr\ (t \le T < t + \Delta t,\ D = k | T \ge t)}{\Delta t}.$$

For subdistributional hazard ratios (HRs), we followed the modeling approach described by Fine and Gray.[26] The subdistributional hazard function focuses on risk of failure from the k^{th} event (k denotes lung cancer death or non–lung cancer death) in subjects who have not yet experienced an event of type k. This is defined as

$$\lambda_k^{sd} = \lim_{\Delta t \to 0} \frac{\Pr\ (t \le T < t + \Delta t, D = k | T > t \cup (T < t \cap K \ne k))}{\Delta t}$$

Time to event was defined as the time interval between blood draw until lung cancer death, other cause of death, or last period of follow-up. Two curves in the cumulative incidence plot were compared using Gray's modified χ^2 test statistics.[27]

All analyses were performed in R (version 4.2.0) using the pROC package for calculating AUC, sensitivity, and specificity metrics, and the cmprisk package for time-dependent survival analyses.

RESULTS

Predictive Performance of the Combined 4MP + $PLCO_{m2012}$ Model for Lung Cancer–Specific Mortality

Of the 552 lung cancer cases diagnosed during the 6-year PLCO study period, 387 (70%) died of lung cancer, 99 (18%) died of other causes, 41 (7%) were still alive at the time of last follow-up, and 25 (5%) did not have survival information available (Table 1; Data Supplement [Table S1]). Of the 2,193 noncase participants, 556 (25%) died of other causes (Data Supplement [Table S2]). Notably, 8 (0.004%) died of lung

TABLE 1. Patient Characteristics and Mortality Outcomes for the PLCO Specimen Set

Variable	Lung Cancer Cases[a]			Noncases[b]	
	Death From Lung Cancer	Death From Other Causes	Not Dead or Missing	Death From Other Causes	Not Dead or Missing
Cases, No.	387	99	66	556	1,629
Sex, No. (%)					
Male	256 (66.1)	68 (68.7)	30 (45.5)	360 (64.7)	845 (51.9)
Female	131 (33.9)	31 (31.3)	36 (54.5)	196 (35.3)	784 (48.1)
Age, years, median (IQR)	66.0 (62.0-69.0)	66 (63.0-70.0)	60.0 (58.0-63.0)	65 (61.0-70.0)	60.0 (57.0-64.0)
Smokers, No. (%)					
Current	173 (44.7)	39 (39.4)	26 (39.4)	134 (24.1)	256 (15.7)
Former	214 (55.3)	60 (60.6)	40 (60.6)	422 (75.9)	1,373 (84.3)
Smoking PYs, median (IQR)	51.0 (39.2-75.8)	52.8 (35.0-78.0)	45.5 (28.0-66.0)	40 (18.5-58.0)	24 (12.0-41.2)
PYs, No. (%)					
<10	5 (1.3)	4 (4)	3 (4.5)	63 (11.3)	323 (19.8)
≥10	377 (97.4)	92 (92.9)	63 (95.5)	478 (86)	1,265 (77.7)
Unknown	5 (1.3)	3 (3)	0 (0)	15 (2.7)	41 (2.5)
Stage, No. (%)					
Early (stage I and II)	106 (27.4)	48 (48.5)	49 (74.2)	—	—
Late (stage III and IV)	237 (61.2)	34 (34.3)	2 (3)	—	—
Unknown	44 (11.4)	17 (17.2)	15 (22.7)	—	—
Subtype, No. (%)					
NSCLC	318 (82.2)	88 (88.9)	64 (97.0)	—	—
SCLC	69 (17.8)	11 (11.1)	2 (3.0)	—	—

Abbreviations: NSCLC, non–small-cell lung cancer; PLCO, Prostate, Lung, Colorectal, and Ovarian; PYs, pack-years; SCLC, small-cell lung cancer.
[a]Lung cancer cases diagnosed within the 6-year PLCO study period.
[b]Eight noncase participants were excluded as they developed lung cancer after the 13-year PLCO study follow-up for lung cancer incidence.

cancer after the 13-year follow-up period for lung cancer incidence. These eight individuals were excluded from subsequent analyses.

Median survival time for lung cancer cases diagnosed within 1 year of blood draw who died of lung cancer was 2.77 years (IQR, 2.60-3.02 years; Data Supplement [Table S4]).

When considering sera collected within 1 year preceding a lung cancer diagnosis and all noncase sera, the combined 4MP + $PLCO_{m2012}$ model had an AUC of 0.88 (95% CI, 0.86 to 0.90) for risk prediction of lung cancer–specific mortality (Fig 1; Data Supplement [Figs S1-S2 and Table S5]). Similar performance estimates were found when considering unique randomly selected case and noncase sera (Data Supplement [Fig S3 and Table S6]). Performance estimates of the combined 4MP + $PLCO_{m2012}$ model for lung cancer–specific mortality from a non–small-cell lung cancer or small-cell lung cancer diagnosis were 0.87 (95% CI, 0.85 to 0.89) and 0.86 (95% CI, 0.82 to 0.90), respectively. Notably, when stratifying individuals into those with COPD and those without COPD, the 4MP + $PLCO_{m2012}$ model yielded respective AUCs of 0.76 (95% CI, 0.69 to 0.84) and 0.88 (95% CI, 0.86 to 0.90) for predicting death due to lung cancer (Data Supplement [Tables S5-S6]).

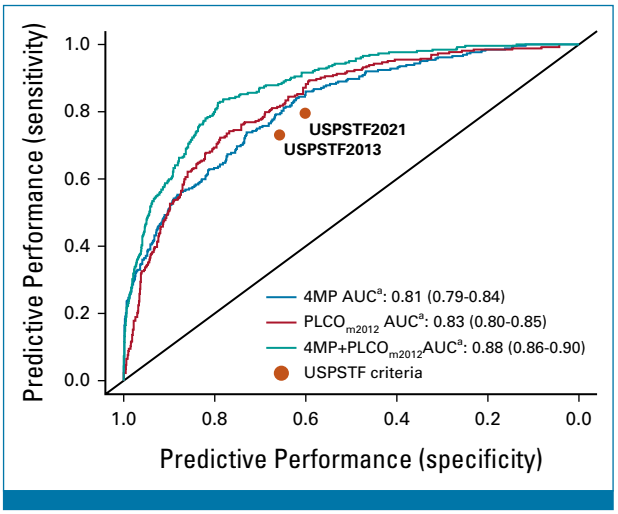

FIG 1. Predictive performance of the 4MP, $PLCO_{m2012}$, and the combined 4MP + $PLCO_{m2012}$ model for predicting lung cancer–specific mortality. Case sera collected within 1 year of diagnosis and all noncase sera were considered. Nodes show corresponding sensitivity and specificity on the basis of USPSTF2013 or 2021 criteria. [a]AUC is in reference to the area under the receiver operating characteristic curve. $PLCO_{m2012}$, Prostate, Lung, Colorectal, and Ovarian risk model; USPSTF, US Preventive Services Task Force.

Comparison of the 4MP + $PLCO_{m2012}$ Model Versus USPSTF Criteria for Predicting Lung Cancer–Specific Mortality Who Smoked ≥10 PYs

We next compared the sensitivity and specificity of the combined 4MP + $PLCO_{m2012}$ model to that of the USPSTF2013 and USPSTF2021 criteria for predicting lung cancer–specific mortality. In comparison with USPSTF2013 criteria, corresponding to ≥1.7% 6-year risk threshold, the combined 4MP + $PLCO_{m2012}$ model had improved sensitivity (85.0 [95% CI, 81.8 to 90.7] *v* 74.0 [95% CI, 68.0 to 79.0]), specificity (71.0 [95% CI, 70.1 to 72.2] *v* 58.0 [95% CI, 57.0 to 59.0]), and positive predictive value (PPV; 24.2% [95% CI, 22.8 to 25.1] *v* 16.3% [95% CI, 15.1 to 17.9]) for predicting lung cancer death (Data Supplement [Tables S7-S9]). At the ≥1.0% 6-year risk threshold, corresponding to the USPSTF2021 criteria, the combined 4MP + $PLCO_{m2012}$ model exhibited overall improved sensitivity of 90.2% (95% CI, 87.1 to 94.2) versus 81.0% (95% CI, 75.7 to 85.0), specificity of 58.1 (95% CI, 56.0 to 59.1) versus 52.0 (95% CI, 50.0 to 53.0), and PPV of 19.3% (95% CI, 18.1 to 20.4) versus 16.0% (95% CI, 13.9 to 17.4) for predicting lung cancer–specific mortality (Data Supplement [Tables S7-S9]).

Relationship of 4MP + $PLCO_{m2012}$ at 1.7% and 1.0% 6-Year Risk Thresholds With Incidence of Lung Cancer Death Among Individuals Who Smoked ≥10 PYs

We further performed lung cancer–specific survival analyses. For these analyses, we considered all case specimens diagnosed within 1 year of blood draw and all noncase individuals with ≥10 PY smoking history dichotomized into test-positive or test-negative on the basis of 4MP + $PLCO_{m2012}$ model scores greater than or equal to or less than the 1.7% or 1.0% 6-year risk thresholds, respectively.

When considering the 1.7% 6-year risk threshold, compared with test-negative PLCO individuals (n = 1,253), the cumulative incidence of lung cancer death was statistically significantly higher in test-positive cases (n = 805; modified χ^2, 277.04; $P < .0001$) with respective subdistributional and lung cancer death–specific HRs of 12.82 (95% CI, 8.67 to 18.77) and 17.08 (95% CI, 9.61 to 10.64; Fig 2; Table 2; Data Supplement [Tables S10-S13 and Figs S4-S7]).

Compared with test-negative cases (n = 990), at the 1.0% 6-year risk threshold, test positive cases (n = 1,068) had a statistically significantly higher cumulative incidence of lung cancer death (modified χ^2, 166.27; $P < .001$) with corresponding subdistributional and lung cancer death–specific HRs of 9.88 (95% CI, 6.44 to 15.18) and 10.65 (95% CI, 6.93 to 16.37), respectively (Fig 2; Table 2; Data Supplement [Tables S10-S13 and Figs S4-S7]).

DISCUSSION

LDCT-based screening for lung cancer has been shown to reduce mortality from lung cancer in multiple large clinical trials. In the United States, the USPSTF currently recommends screening for individuals with ≥20 PY smoking history, age 50 years and older, and quit date <15 years. Despite these recommendations, enrollment in LCS in the United States has been low.[28,29] Worldwide, CT-based screening is gaining further acceptance, but patient and provider concerns remain false-positive tests and overdiagnosis.[30]

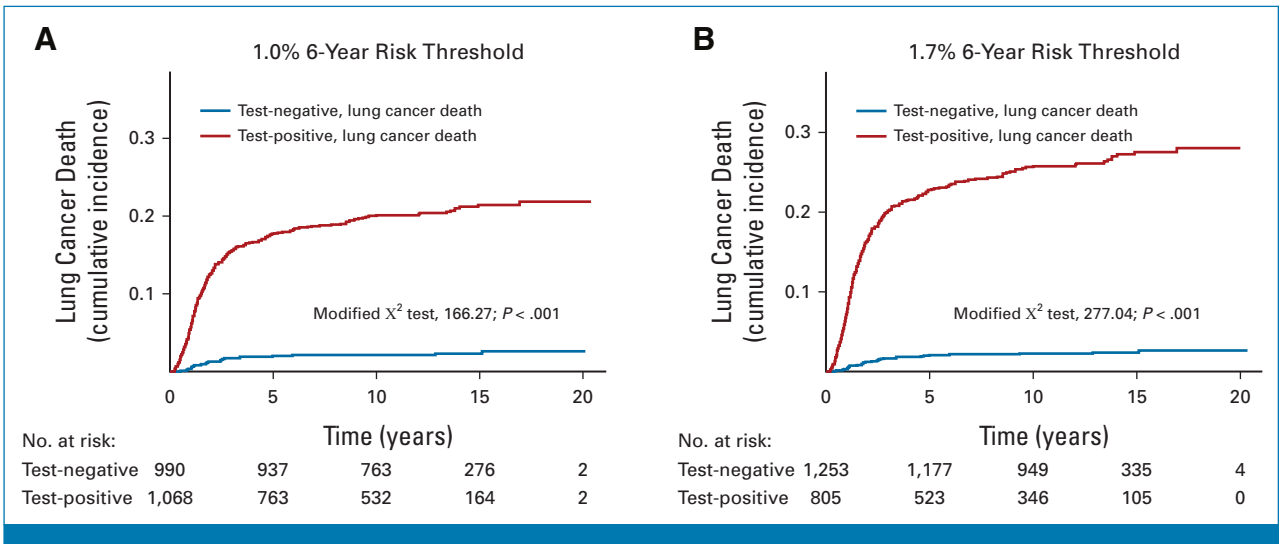

FIG 2. Cumulative incidence plot for lung cancer death for individuals who were test-positive or test-negative on the basis of 4MP + $PLCO_{m2012}$ scores greater than or equal to or less than the (A) 1.0% and (B) 1.7% 6-year risk thresholds. Analyses were based on cases diagnosed within 1 year of blood draw and all noncase participants with ≥10 PY smoking history. 4MP, four-marker protein panel; $PLCO_{m2012}$, Prostate, Lung, Colorectal, and Ovarian risk model; PYs, pack-years.

TABLE 2. Subdistributional Hazard Model and Cause-Specific Hazard Model Ratios for Individuals With ≥10 PY Smoking History at 1.0% and 1.7% 6-Year Risk Thresholds

			Subdistributional Hazard Model				Cause-Specific Hazard Model			
			Lung Cancer Death		Death From Other Causes		Lung Cancer Death		Death From Other Causes	
Risk Threshold	Criteria[a]	No. at Risk at Baseline[b,c]	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
1.7% risk threshold	USPSTF2013	Test-positive = 978	3.78 (2.82 to 5.06)	<.001	1.60 (1.34 to 1.89)	<.001	3.93 (2.93 to 5.26)	<.001	1.94 (1.63 to 2.31)	<.001
		Test-negative = 1,083								
	$PLCO_{m2012}$	Test-positive = 869	6.25 (4.56 to 8.57)	<.001	2.1 (1.77 to 2.49)	<.001	6.69 (4.88 to 9.17)	<.001	2.74 (2.30 to 3.26)	<.001
		Test-negative = 1,189								
	4MP	Test-positive = 926	8.78 (6.08 to 12.66)	<.001	1.64 (1.38 to 1.94)	<.001	9.39 (6.51 to 13.55)	<.001	2.14 (1.80 to 2.54)	<.001
		Test-negative = 1,132								
	4MP + $PLCO_{m2012}$	Test-positive = 805	12.82 (8.76 to 18.77)	<.001	2.22 (1.87 to 2.62)	<.001	14.08 (9.61 to 20.64)	<.001	3.18 (2.67 to 3.78)	<.001
		Test-negative = 1,253								
1.0% risk threshold	USPSTF2021	Test-positive = 1,118	4.27 (3.07 to 5.94)	<.001	1.46 (1.23 to 1.74)	<.001	4.41 (3.18 to 6.14)	<.001	1.76 (1.47 to 2.09)	<.001
		Test-negative = 943								
	$PLCO_{m2012}$	Test-positive = 1,223	7.91 (5.06 to 12.33)	<.001	2.50 (2.05 to 3.06)	<.001	8.40 (5.37 to 13.14)	<.001	3.08 (2.52 to 3.77)	<.001
		Test-negative = 835								
	4MP	Test-positive = 1,236	11.15 (6.61 to 18.79)	<.001	1.94 (1.61 to 2.34)	<.001	11.82 (7.01 to 19.93)	<.001	2.40 (1.98 to 2.91)	<.001
		Test-negative = 822								
	4MP + $PLCO_{m2012}$	Test-positive = 1,068	9.88 (6.44 to 15.18)	<.001	2.62 (2.17 to 3.15)	<.001	10.65 (6.93 to 16.37)	<.001	3.37 (2.78 to 4.07)	<.001
		Test-negative = 990								

Abbreviations: 4MP, four-marker protein panel; HR, hazard ratio; $PLCO_{m2012}$, Prostate, Lung, Colorectal, and Ovarian risk model; PY, pack-year; USPSTF, US Preventive Services Task Force.

[a]Model scores for the 4MP as well as from the logistic regression model that combines the 4MP with $PLCO_{m2012}$ were applied as described in our prior publication.[16]

[b]Test-positive cases are defined as those individuals with 4MP, $PLCO_{m2012}$, or 4MP + $PLCO_{m2012}$ scores >1.7% and 1.0% 6-year risk thresholds. Test-negative are cases are those with scores ≤1.7% and 1.0% 6-year risk thresholds.

[c]Forty-two individuals lacked sufficient information to calculate $PLCO_{m2012}$.

Additional barriers to LCS include access to and awareness of LCS programs, costs of implementation, amount of workload introduced into health care systems, and fear of cancer diagnosis and treatment.[29-31]

Individualized risk-based approaches to improve screening selection offer potential for a more favorable trade-off between harms and benefits of LCS. Several risk models have been developed to assess an individual's risk of lung cancer incidence or lung cancer death, which are highly correlated. However, limited studies have evaluated the contributions of blood-based biomarkers for risk assessment of lung cancer death in the preclinical setting, because of the necessity for availability of prediagnostic blood specimens with the adequate follow-up mortality to collect mortality outcomes. Participants in the PLCO trial were followed for up to 20 years after enrollment, with significant effort devoted to accurate documentation of causes of death. The PLCO cohort is thus well suited to assess the contributions of blood-based biomarkers for predicting lung cancer incidence as well as lung cancer death.

In our prior study, we reported that the 4MP in combination with the $PLCO_{m2012}$ risk model substantially improved sensitivity and specificity compared with USPSTF criteria for risk assessment of lung cancer incidence.[16] In the current study, we demonstrated mortality benefit of the 4MP. Specifically, we reported that the 4MP + $PLCO_{m2012}$ better predicts lung cancer–specific mortality compared with USPSFT criteria, yielding improvements in sensitivity, specificity, and PPV. For additional comparison, in the PLCO cohort, the LCDRAT model had a reported AUC of 0.81 (95% CI, 0.79 to 0.83) for predicting lung cancer death among those with smoking history.[14] Here, we show that the 4MP + $PLCO_{m2012}$ model yielded an AUC of 0.88 (95% CI, 0.86 to 0.90) for predicting lung cancer–specific mortality among ever-smoker individuals.

In the United States, we envision that testing of the 4MP would be useful for individuals who are currently eligible for LDCT screening and expanded to additionally include individuals who have ≥10 PY smoking history. Individuals identified to be at high risk of lung cancer incidence or death, on the basis of 4MP + $PLCO_{m2012}$ scores ≥1.0% 6-year risk, corresponding to USPSF2021 criteria, would be referred to LDCT through shared decision making. Uptake to LCS programs, even for those eligible, has stubbornly remained below 15%, and a positive biomarker test may act as additional impetus for eligible individuals to undergo screening.[31]

For those individuals who lack sufficient information required for $PLCO_{m2012}$, the 4MP alone may be used to inform on the need for LDCT on the basis of the individual's risk profile. Our previous work demonstrated that 4MP values exponentially increase the closer the blood sample is taken to when lung cancer is clinically diagnosed. Thus, testing of 4MP should be performed regularly with testing intervals matching their degree of risk.[24]

For countries outside of the United States that have not yet adopted USPSFT2021 criteria or that have not implemented LCS, the improved performance of the 4MP + $PLCO_{m2012}$ at the more stringent decision-making threshold of ≥1.7% 6-year risk may select for individuals at exceptionally high risk of lung cancer death who would benefit from LDCT while limiting the number of false-positives associated with a lower risk threshold.

There are considerations to our study. In the PLCO trial, participants did not undergo routine LDCT screening.[32] Consequently, the benefits associated with CT-based screening, including newer guidelines for nodule management of CT findings (eg, Lung CT Screening Reporting & Data System),[33] were not able to be assessed. Instead, diagnoses of lung cancer were presumably a combination of individuals found to have abnormalities by chest radiography and those presenting with symptoms necessitating further workup. Given the lack of sensitivity of chest X-ray for early-stage disease, a higher proportion of participants were diagnosed with advanced-stage disease in the PLCO than would be expected in a CT-based LCS program.

Although we acknowledge that the contributions of the 4MP + $PLCO_{m2012}$ model for risk-based referral needs to be evaluated in the context CT-based screening, we anticipate that implementation of the 4MP + $PLCO_{m2012}$ model in the PLCO cohort would have resulted in a potential stage shift, where patients are more likely to benefit from curative-intent treatment. Another consideration is lack of non-screening arm, preventing us from calculating pertinent clinical metrics such as number of lung cancer deaths averted or the number of screens needed to prevent one lung cancer death.

In conclusion, the 4MP + $PLCO_{m2012}$ model offers improved means for individualized risk assessment for lethal lung cancers, compared with current USPSTF criteria. The test has potential to better select for individuals who would benefit from LDCT screening.

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DISCLAIMER

The statements contained herein are solely those of the authors and do not represent or imply concurrence or endorsement by the National Cancer Institute.

EQUAL CONTRIBUTION

E.I. and J.F.F contributed equally to this work as co-first authors.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

Relevant data supporting the findings of this study are available within the article and Data Supplement. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Mortality Benefit of a Blood-Based Biomarker Panel for Lung Cancer on the Basis of the Prostate, Lung, Colorectal, and Ovarian Cohort

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Johannes F. Fahrmann
Patents, Royalties, Other Intellectual Property: There is IP related to biomarkers for early detection of pancreas cancer

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Patents, Royalties, Other Intellectual Property: I am one of the co-inventors for a biomarker panel for pancreatic cancer. The patent was filed by the UT MD Anderson Cancer Center and was licensed to a company by the UT MD Anderson Cancer Center, I am a co-inventor for a biomarker test. UT MDACC own the IP. I received a license fee in January 2019. No other payment has been received after that

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